JAN 18 1983

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

JAN 7 1983

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MEMORANDUM JAN 7

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

TO: H. Jacoby, Product Manager #21
Registration Division (TS-767)

THRU: Edwin R. Budd, Section Head
Section II, Toxicology Branch
Hazard Evaluation Division (TS-769) Budd 1/7/83

THRU: Orville E. Paynter, Chief OEP 1/7/83
Toxicology Branch
Hazard Evaluation Division (TS-769)

SUBJECT: PP 6F1748. Benomyl on Small Grains, Liver and Milk.

TOX Chem No. 75A

Action Requested:

DuPont has submitted a revised Section F to propose the establishment of tolerances for Benomyl and its metabolites containing the benzimidazole moiety (calculated as Benomyl) as follows:

Wheat, oats, barley, rye (grain form)	0.2 ppm
Oats, barley, rye (straw)	0.2 ppm
Wheat (straw)	15.0 ppm

and revised tolerances as follows:

Liver (cattle, goats, horses, sheep, hogs)	4.0 ppm
Milk	1.0 ppm

Recommendations:

1. Toxicology Branch (TB) objects to the proposed tolerances.

2. The incremental increase in TMRC resulting from these additional tolerances is 19.16% (see attached computer printout). TB considers this increase in dietary exposure to be highly significant.

3. Because Benomyl is capable of producing teratogenic, spermatogenic and oncogenic effects, the proposed tolerance of 1.0 ppm in milk poses significant risks of such effects to groups which consume large quantities of milk, such as children and pregnant women.

4. Calculations for the MOS (margins of safety) for the teratogenic effect, using a provisional NOEL of 30 mg/kg/day and single small serving size exposures, reveal a range of values from 2,654 for liver to 150,000 for whole wheat or rye bread.

DuPont has agreed to conduct and submit to EPA a new rat teratology study in order to establish a firmer NOEL for this effect (see DuPont letter, dated 1/6/82). This study has been received by EPA, but is incomplete.

5. Benomyl is oncogenic in mice. The lifetime risk of cancer from all published tolerances excluding the proposed tolerances is 7.5×10^{-5}. The incremental increase from the present action is .0000145. This increase elevates the overall lifetime oncogenic risk to 8.95×10^{-5} or essentially 1×10^{-4}.

6. Benomyl has induced significant adverse effects in reproduction studies. The most notable of these effects were damage to spermatogonia and seminal vesicles. The NOEL for these effects is 7.5 mg/kg/day.

This NOEL, for a 60 kg man, would be 7.5x60 = 450 mg/day. The overall TMRC (including these proposed tolerances) is 2.61 mg/day. The MOS for reproductive effects, then, is 450 mg/day divided by 2.61 mg/day = 172.

7. TB considers the significantly increased exposure (19.16% increase in TMRC), the significant increase in risk for groups consuming large quantities of milk, the MOS (single small servings) for teratas of 2,654 to 150,000, the failure of DuPont to date to submit the completed rat teratology study, the increased lifetime overall risk for cancer approaching 1×10^{-4} and the MOS for reproductive effects of 172 to be sufficient reason to reject the proposed tolerances for Benomyl on small grains, liver and milk.

8. RCB has raised a question concerning the toxicological significance of the n-C_4H_9N moiety of Benomyl formed during Benomyl metabolism (reviews of P. V. Errico, 3/14/80; L. S. Probst, 1/31/80; and J. W. Holder, 8/10/79). Since this moiety is presumably formed in experimental animals (as indirectly evidenced by the formation of MBC in these animals; refer to H. D. Sigler, Antifungal Compounds, Vol. 2 Marcel Dekker, Inc., 1977.), Toxicology Branch believes the toxicology of this moiety to have been adequately evaluated during the testing of the parent compound. This moiety, therefore, is of no toxicological concern at this time.

A discussion of information considered in deriving this recommendation is given below.

1. Background:

Benomyl is an RPAR chemical. A comprehensive review of the data available for the chemical was conducted in connection with the Rebuttable Presumption Against Registration (RPAR) for Benomyl which was published in the Federal Register of December 6, 1977 (42 FR 61788).

This presumption was based on information indicating that Benomyl posed the risks of mutagenicity (point mutation and non-disjunction), spermatogenic depression and teratogenic effects, acute toxicity to aquatic organisms and significant population reduction in nontarget organisms. In the Federal Register of August 30, 1979 (44 FR 51166), the Agency issued a Preliminary Notice of Determination, which concluded that Benomyl continued to pose the risks noted above with the exception of point mutations and significant population reductions in nontarget organisms. In this Notice and the accompanying Position Document 2/3, the Agency weighed the risks and benefits of use together and determined that certain modifications to the terms and conditions of use were necessary to reduce the risks of use to applicators.

Subsequent to these findings, data have become available which indicate that Benomyl is oncogenic in mice. Additional teratogenic tests have also been submitted. A review of the presently registered uses and proposed uses of Benomyl in light of the potential oncogenic, reproductive and teratogenic adverse effects has been completed. The Agency's position concerning the RPAR issues with Benomyl will be published in the near future.

2. Studies Considered for the Present Tolerances on Small Grains, Liver and Milk.

The scientific data considered in support of this tolerance include a 2-year dog feeding study with a no-observed-effect level (NOEL) of 500 ppm; a 2-year rat feeding study with a NOEL of 2500 ppm; a 3-generation

rat reproduction study with a NOEL of 100 ppm and two teratology studies, one on rats with a NOEL of 129 mg/kg and another on rabbits with a NOEL of 500 ppm.

Based on Toxicology Branch calculations using the 3-generation reproduction rat study with a NOEL of 100 ppm and employing a 100-fold safety factor, the allowable daily intake (ADI) for Benomyl is 0.05 mg/kg/day and the maximum permissible intake (MPI) is 3.00 mg/day for a 60 kg person. Established and pending tolerances result in a theoretical maximum residue contribution (TMRC) of 2.1905 mg/day and utilization of 73.02 % of the ADI. The proposed tolerances on small grains, liver and milk would result in an increase in the TMRC of 0.41955 mg/day, bringing the total TMRC to 2.6101 mg/day (an incremental increase of 19.16%) utilizing 87.00% of the ADI. Tolerances previously established for Benomyl and its metabolites and those pending are also shown on the attached printout.

3. Teratogenicity Risks:

The risk of teratogenicity from small single servings of small grains commodities, milk and liver to a pregnant 60 kg woman as calculated against a provisional NOEL of 30 mg/kg (memo of E. Johnson, EPA, September 24, 1981 to B. Julin, Regulatory Affairs, E. I. Dupont de Nemours and Company) is provided below. The margins of safety for ingestion of Benomyl-treated commodities range from 2,654 (liver) to 150,000 (rye or whole wheat bread). Ingestion of more than two-three servings of milk would significantly decrease the MOS. The MOS may also be affected when the promised teratogenicity study (letter of B. Julin, E. I. Dupont de Nemours, to Margaret Jones, SPRD, EPA, September, 1981) provides a more definitive teratogenicity NOEL.

Teratogenicity Risk from Single Serving of Benomyl-Treated Small Grain Commodities, Milk and Liver

Commodity	Serving Size*	Wt. kg*	Tolerance ppm	Benomyl		Margin of Safety (30 mg/kg NOEL divided by mg/kg body weight)
				mg/serving	mg/kg B.W. (BW= 60 kg)	
Liver	3 oz	.170	4.0	0.680	0.0113	2,654
Milk	1 cup	.244	1.0	0.244	0.004	7,500
Wheat	2 slices whole wheat bread	.056	0.2	0.0112	0.0002	150,000
Oats	1 cup cooked oatmeal	.245	0.2	0.049	0.0008	37,500
Rye	rye bread 2 slices (2/3 wheat 1/3 rye flour)	.050	0.2	0.0100	0.0002	150,000
Barley	1 cup cooked	.200	0.2	0.0400	0.0007	42,857

* From: Nutritive Value of American Foods, Agriculture Handbook No. 456, USDA, Wash. D.C., 1975.

4. Cancer Risk:

The anticipated life-time cancer risk from all established tolerances (treated feed commodities) is 7.5×10^{-5}. This is based on a total diet, maximum residue exposure assumption using the metabolite, MBC mouse feeding study. The incremental increase in risk from these proposed tolerances is 1.45×10^{-5} which brings the total overall lifetime risk to 8.95×10^{-5} or roughly 1×10^{-4}.

Calculations:

a.

Commodity	Increased Tolerance *	Food Factor	mg Benomyl/ day/person
Liver	3.8 ppm	0.03	0.00171
Milk	0.9 ppm	28.62	0.38631
Wheat	0.2 ppm	10.36	0.03109
Oats	0.2 ppm	0.36	0.00107
Barley	0.2 ppm	0.03	0.00009
Rye	0.2 ppm	0.03	0.00009
			0.42036

* includes all proposed increases for commodity above presently established tolerances.

b. For a 60 kg individual, $\frac{0.42036}{60}$ = 0.007006 mg/kg/day exposure

c. Incremental Lifetime risk = Q_1 ($= 2.065 \times 10^{-3}$) x Exposure (0.007006)
= 0.0000145

d. Lifetime risk from previous published tolerances, all dietary sources = 7.5×10^{-5}.

e. Life time risk (including above proposed tolerances) = 0.000075 + 0.0000145
= 0.0000895
= 8.95×10^{-5}

5. Reproductive Margin of Safety:

The Margin Of Safety (MOS) for reproductive effects (damage to spermatogonia and seminal vesicles) for a 60 kg man as calculated against a NOEL of 7.5 mg/kg/day is provided below. The overall MOS for ingestion of all Benomyl-treated RAC's (including these proposed tolerances) is 172.

NOEL = 7.5 mg/kg/day (See TB review dated 6/23/82, by Chris Chaisson, copy attached)

For a 60 kg man, NOEL = 7.5 x 60 = 450 mg/day. Overall TMRC = 2.61 mg/day. (See computer printout, attached)

Margin of Safety = 450 divided by 2.61 = 172.

Minnie Sochard, Ph.D. Minnie Sochard 1/5/83
Toxicology Branch
Hazard Evaluation Division (TS-769)

Attachment

OPP:HED:TOX: M.SOCHARD:sb 12/23/82 X71511 Rm 824 #m16

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NOEL change not recorded per

File last updated 12/10/82

ACCEPTABLE DAILY INTAKE DATA

RAT,Older NOEL mg/kg	NOEL ppm	S.F.	ADI mg/kg/day	MPI mg/day(60kg)
5.000	100.00	100	0.0500	3.0000

Published Tolerances

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Pineapple(123)	35.000	0.30	0.15560
Apricots(3)	15.000	0.11	0.02529
Cherries(30)	15.000	0.10	0.02299
Nectarines(100)	15.000	0.03	0.00675
Peaches(114)	15.000	0.90	0.20235
Plums,inc prunes(125)	15.000	0.13	0.02989
Citrus Fruits(33)	10.000	3.81	0.57179
Grapes, not raisins(67)	10.000	0.45	0.06745
Raisins(134)	50.000	0.04	0.03066
Mushrooms(97)	10.000	0.03	0.00450
Blackberries(15)	7.000	0.03	0.00315
Blueberries(18)	7.000	0.03	0.00315
Boysenberries(17)	7.000	0.03	0.00315
Dewberries(52)	7.000	0.03	0.00315
Loganberries(86)	7.000	0.03	0.00315
Raspberries(135)	7.000	0.03	0.00315
Apples(2)	7.000	2.53	0.26565
Pears(116)	7.000	0.26	0.02683
Rice(137)	5.000	0.55	0.04139
Strawberries(152)	5.000	0.18	0.01380
Tomatoes(163)	5.000	2.87	0.21561
Celery(28)	3.000	0.29	0.01288
Mangoes(88)	3.000	0.03	0.00135
Beans(9)	2.000	2.04	0.06120
Bananas(7)	0.200	1.42	0.00426
Avocados(6)	3.000	0.03	0.00135
Cucumbers,inc pickl(46)	1.000	0.73	0.01088
Melons(92)	1.000	2.00	0.03005
Pumpkin,inc squash(131)	1.000	0.11	0.00169
Summer Squash(155)	1.000	0.03	0.00045
Wintersquash(171)	1.000	0.03	0.00045
Peanuts(115)	0.200	0.36	0.00107
Soybeans (oil)(148)	0.200	0.92	0.00275
Sugar,cane&beet(154)	0.200	3.64	0.01091
Nuts(101)	0.200	0.10	0.00031
Eggs(54)	0.100	2.77	0.00416
Meat,inc poultry(89)	0.100	13.85	0.02077
Corn,sweet(40)	0.200	1.43	0.00429
Sweet Potatoes(157)	0.200	0.40	0.00120
Eggplant(53)	0.200	0.03	0.00009
Peppers(120)	0.200	0.12	0.00037
Broccoli(19)	0.200	0.10	0.00031
Brussel Sprouts(20)	0.200	0.03	0.00009
Cauliflower(27)	0.200	0.07	0.00021
Chinese Cabbage(177)	0.200	0.03	0.00009
Collards(37)	0.200	0.08	0.00025

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Garlic 31)	0.200	0.03	0.00009
Kale(75)	0.200	0.03	0.00009
Kohlrabi(76)	0.200	0.03	0.00009
Mustard Greens(99)	0.200	0.06	0.00018
Spinach(150)	0.200	0.05	0.00015
Turnips(165)	0.200	0.05	0.00015
Turnip Greens(166)	0.200	0.05	0.00015
Rutabagas(139)	0.200	0.03	0.00009
Cabbage,sauerkraut(22)	0.150	0.74	0.00333
Milks(93)	0.100	28.62	0.04292

MPI	TMRC	% ADI
3.0000 mg/day(60kg)	1.9170 mg/day(1.5kg)	63.90

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Unpublished,Tox Approved E2409,6F1707,1810,6E1342,1837,2469

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Onions(105)	1.000	0.83	0.01242
Yams(Yautia)(199)	0.200	0.03	0.00009
Carrots(24)	0.200	0.48	0.00144
Beet greens(13)	10.000	0.03	0.00450
Beets(14)	0.200	0.17	0.00052
* Liver(211)	1.800	0.03	0.00081
* Lettuce(84)	10.000	1.31	0.19622
* Papayas(109)	3.000	0.03	0.00135
* Currants(48)	7.000	0.03	0.00315
*Cabbage,sauerkraut(22)	4.800	0.74	0.05298

MPI	TMRC	% ADI
3.0000 mg/day(60kg)	2.1905 mg/day(1.5kg)	73.02

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Current Action 6E1748

CROP	Tolerance	Food Factor	mg/day(1.5kg)
* Liver(211)	2.000	0.03	0.00090
* Milk&Dairy Products(93)	0.900	28.62	0.38631
* Wheat(170)	0.200	10.36	0.03109
* Oats(102)	0.200	0.36	0.00107
* Barley(8)	0.200	0.03	0.00009
* Rye(140)	0.200	0.03	0.00009

MPI	TMRC	% ADI
3.0000 mg/day(60kg)	2.6101 mg/day(1.5kg)	87.00

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% Increase to the TMRC = $\frac{2.6101 - 2.1905}{2.1905} \times 100 = 19.16\%$

* Toxicology Branch has deferred to the Administrator the acceptability of the increased incremental risk associated with each of these proposed tolerances.